CALIFORNIA DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

METHYLISOTHIOCYANATE (MITC)

SB 950-295, Tolerance # 50334

JANUARY 16, 1987
Revised 8/10/87, 4/28/89, 8/8/91

I. DATA GAP STATUS

Combined, rat: No data gap, no adverse effect

Chronic dog: Data gap, inadequate study, possible adverse effect indicated[a]

Onco mouse: No data gap, no adverse effect

Repro rat: Data gap, inadequate study, possible adverse effect indicated[b]

Terato rat: No data gap, no adverse effect

Terato rabbit: No data gap, no adverse effect

Gene mutation: No data gap, possible adverse effect[a]

Chromosome: No data gap, possible adverse effect[a]

DNA damage: No data gap, no adverse effect

Neurotox: Not required at this time

----------**Note, Toxicology one-liners are attached**

** indicates acceptable study
Bold face indicates possible adverse effect
File name T910808
Revised 8/8/91 by M. Silva.
NOTE: Methylenebis(thiocyanate) (SB 748) is grouped with methylisothiocyanate (SB 295) and 2-(2-butoxyethoxy) ethyl thiocyanate (SB 545). See the respective "Summary of Toxicology Data" for the one-liners for the compounds other than MITC.
a - The possible adverse effects (chronic dog, gene mutation and chromosomal aberration) were reported for methylenebis(thiocyanate), SB 748.

b - There are insufficient data to determine whether or not a treatment related effect is occurring in this study (MITC only). See 1-liner.

Record numbers rectified with Library printout through 50271-024 and 50334-010 and 50046-016.

II. TOXICOLOGY SUMMARY

COMBINATION, RAT

** 008 037177 "Methyl Isothiocyanate: A Chronic Oral (Drinking Water) Toxicity and Carcinogenicity Study in the Rat." (4/1981, Hazleton Europe, T27) Rat-CD; MITC, 95-96%; 60/sex/group were given 0, 2, 10 or 50 ppm in the drinking water over 2 years; 5/cage; nominal sys NOEL = 10 ppm (decreased food consumption, water intake and decreased weight gain in males), actual NOEL closer to 8 ppm based on analyses of the drinking water; onco NOEL $\geq$ 50 ppm; no adverse chronic/onco effect reported; initially reviewed as unacceptable because of problems with stability in first 10 weeks of study when test article was shipped in metal cans - this should have been resolved before initiation of study - also, should have data on content in water before week 23 and justification of dose selection with marginal evidence of toxicity. Submission of additional data in 50334-010, stability and analyses of drinking water in depth and an addendum to protocol variations in the study, upgrades the study to acceptable status with no adverse effect noted. It is unlikely that a much higher dose could have been used based on the decreased water intake at 50 ppm. Gee, 5/13/86 and 8/7/87.

010 053185, 053186, 053189, 053190 Determination of the stability and solubility of MITC in laboratory animal drinking water for 037177. Gee, 8/7/87.

010 053191 and 053192 Amendments to protocol for 037177.

50046-016 004281 (No date given, Nor-am) Very brief summary of 037177.

CHRONIC, DOG

No studies currently on file. Nor-Am has requested a waiver for this requirement.

"Methyl Isothiocyanate 1 Year Oral Toxicity Study in Beagle Dogs (Final Report)," (Harling, R.J., Barker, M.H., Brown, J.M., Buist, D.P., Crook, D., Majeed, S., and Gopinath, C., Huntingdon Research Centre, Ltd., England, 1989). Methyl isothiocyanate technical (purity = 95.64%; Batch #'s: CR 18642/1 & CR18642/2) was administered by oral gavage as an MITC suspension (corn oil vehicle) at 0, 0.04, 0.4 and 2.0 mg/kg/day to 6 Beagle dogs/sex/dose for 52 weeks. The required volumes were given as two daily doses at 4-5 hours between subdoses. Suspensions in corn oil of 0.0004, 0.004, and 0.02 g% MITC were given in a volume of 5.0 ml/kg and and flushed down with 20 ml tap water until day 2 of week 15. From day 3 of week 15, the dose was changed to 0.25 ml/kg, with a change of MITC in corn oil to 0.008, 0.8, and 0.4 g% (flushed down with an equal volume of corn oil). No adverse effect indicated. In the report it was stated that many of the effects, such as vomiting, excessive salivation, liquid feces, and decreased food consumption were due to the corn oil vehicle. The effects seemed related to dose, however, and therefore, they appear to be treatment related. Vomiting and increased salivation may be related to irritation caused by the compound as it is broken down in the acidic environment in the stomach. It could also have to do with the toxic effects of thiocyanate, which include vomiting and excessive salivation. Thiocyanate, which reacts with oxygen binding sites in red blood cells would also induce hemolysis, accompanied by a decrease in packed cell volume, hemoglobin and red blood cells. These effects were observed in the study. There were no ECG effects in the dogs, however this would not be expected unless acute, high doses were used. NOEL = 0.4 (Increased vomiting, salivation and loose stool; decreased body weight gain; decreased food consumption--primarily males; increased male liver weights; decreased packed cell volume, hemoglobin and RBCs, increased platelets and activated partial thrombplastin time in males and decreased total protein and albumin in both sexes.) **These data were not evaluated for the purpose of filling the chronic dog data gap.** M. Silva, 7/25/91.

ONCOGENICITY, RAT

See under Combined Rat above.

ONCOGENICITY, MOUSE

** 007 037176 "Two-Year Chronic Oral Toxicity and Oncogenicity Study with Methyl Isothiocyanate in Albino Mice." (12/1980, Nippon Experimental Medical Research Institute, T52) Mice-ICI:JCR; MITC, 93.14%, lot #MS 25206; 70/sex/group given 0, 5, 20, 80 or 200 ppm in drinking water over two years; nominal sys NOEL = 20 ppm (3.48 mg/kg mean) (decreased water intake, decreased body weight gain, clinical obs of raised hair, dull coat); actual NOEL somewhat less; no chronic or onco effect due to a.i. is reported. Initially reviewed as unacceptable with no analysis of dosing water for content or stability over 24-hour period, solubility in water was not addressed. With submission of 50334-010, record nos. 053183, 053184, 053187 and 053188, the study has been upgraded to acceptable status with no oncogenic effect reported. Gee, 5/12/86 and 8/7/87.

010 053183, 053184, 053186 Reports on stability and solubility of MITC in drinking water for 037176.

010 053187, 052188 Three-week subchronics justifying dose selection for 03176.

006 037165 (1985, Nippon Experimental Medical Research Institute) Addendum to and reviewed with 007 037176 (eye report, tissue inventory and histopathology corrections). Gee, 5/12/86.

50046-016 033906 (No date given, Nor-Am) Very brief summary of 037176. Gee, 7/25/85.

REPRODUCTION, RAT

013 074316 "Technical Methylisothiocyanate (MITC): 2 Generation Oral (Drinking Water) Reproduction Study in the Rat," (Barker, L., Hazleton UK, Report No. TOX/87/203-21, 12-87). Technical methylisothiocyanate Purity = 95.86-96.51%) was administered to Spraque Dawley rats in drinking water at 0, 2, 10 or 50 ppm for 2 generations (P0 generation = 30/sex/group; F1 generation = 25/sex/group). For males this was equivalent to 0, 0.16, 0.7 or 3.49 mg/kg/day, for females it was 0, 0.20, 0.94 or 4.49 mg/kg/day. Parental NOEL = 2 ppm (There was a significant decrease in water consumption in P0 & F1 at $\geq$ 10 ppm. Group mean body weights were reduced in both sexes of both generations at 50 ppm. There were increases in some organ weights and organ/body weight ratios in both sexes of P0 & F1.) Reproduction NOEL cannot be determined until the historican controls for pup viability and preweaning loss % have been received and evaluated. The study shows indications of reduced pup viability and an increase in preweaning loss % in the F1 & F2 pups. **Possible adverse effect.** Currently, there is insufficient information to determine whether or not this was a treatment-related effect.) **Not Acceptable** (Historical controls are requested for pup viability and preweaning loss % as well as an explanation for these effects. Histology was performed on only 10/sex/group, an explanation is requested for the selection process.) M. Silva, 7/18/91.

50046-016 004279 (No date given, Nor-Am) Very brief summary: Rat-CD; MITC, no purity given; doses tested were 0, 1, 3 and 10 mg/kg by oral gavage. Decrease in body weight gain at 3 and 10 mg/kg. Incomplete and unacceptable (insufficient data). Gee, 7/25/85.

TERATOLOGY, RAT

** 006 037167 "Methyl Isothiocyanate (MITC) Oral (Gavage) Teratology Study in the Rat - Final Report." (2/1983, Hazleton.) Rat - Sprague Dawley (Crl:CD(SD)Br); MITC, ~ 95%, Batch # R27/S 6350; 24-28/group given 0, 1, 5 or 25 mg/kg by oral gavage in corn oil, 6-15 days of gestation; maternal NOEL = 1 mg/kg (maternal body weight decreased gain); developmental toxicity NOEL = 5 mg/kg (slightly decreased fetal weight but live fetuses/dam also higher); no developmental tox effect; complete and acceptable. Gee, 5/13/86.

TERATOLOGY, RABBIT

** 006 037166 "Methyl Isothiocyanate (MITC) Oral (Gavage) Teratology Study in the New Zealand White Rabbit - Final Report." (1984, Hazleton.) Rabbit-New Zealand White; MITC ~ 96%; 16/group were given 0, 1, 3 or 5 mg/kg by oral gavage in corn oil; maternal NOEL = 3 mg/kg (body weight decrease in gain, decreased food consumption days 7 - 19; no developmental toxicity without maternal effects - developmental toxicity NOEL = 3 mg/kg (reduction in mean fetal weight at 5 mg/kg but also larger litter size); complete, acceptable.
Gee, 5/13/86.

004 014992 (1984, Hazleton) Gee, 7/25/85. Summary of 006 037166.

50046-016 004278 (No date or lab given.) Very brief summary: Rabbit - albino; MITC, no purity given; doses tested were 0, 1, 3 and 10 mg/kg in gelatin tablets given orally. Maternal toxicity at 3 and 10 mg/kg. NOEL = 1 mg/kg. Insufficient data to evaluate for adverse effect. Incomplete, unacceptable (no data presented). Gee, 7/25/85 and 5/19/86.

MUTATION, GENE

Microbial Systems

006 037171 "Mutagenicity Screening Studies on Pesticides." (1981, publication in Environmental Mutagen Carcinog. Pro. Intl. Conf, 3rd: 331 - 335 (1981) by Y. Shirasu et al.) MITC was not reported as a mutagen in Salmonella (strains used not clear) or E. coli WP2 hcr. Gee, 5/12/86.

006 037172 "Further Mutagenicity Studies on Pesticides in Bacterial Reversion Assay Systems." (1983, publication in Mutation Research 116: 185 - 216 (1983) by M. Moriya et al.) A total of 228 pesticides including MITC were screened in Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100 and in E. coli WP2 hcr with and without activation to 5000 ug/plate. MITC was not reported as a mutagen. This article appears to be the same study as #037171. Unacceptable due to lack of data. Gee, 5/12/86.

006 037174 "Microbial Mutagenicity Testing on Methyl Isothiocyanate." (1978, Institute of Environ. Tox., Japan) MITC, 94.78%; Salmonella, TA1535, TA1537, TA1538, TA98 and TA100; ± S-9 at 0, 0.5, 1, 5, 10, 50, 100, 500 or 1000 ug/disk in modification of Ames assay; no increase in reversion rate is reported; unacceptable (no repeat trial obvious, report not clear on positive controls and volatility properties.) Gee, 5/12/86.

006 037175 "Testing for Mutagenic Activity of ZK 3.318." (1976, Inveresk Research Int'l - Scotland, IRI Project No. 407071) Salmonella, TA1535, TA1537, TA1538, TA98 and TA100; MITC, no purity given, lot # 8042; with and without mouse liver S-9 at 0, 5, 25, 125 and 500 ug/plate and 2.5 mg/plate, one trial, one plate; inadequate positive controls; unacceptable (no repeat trial, single plate, inadequate positive controls without activation, justification for using mouse liver (minor variation). Gee, 5/12/86.

50046-016 004273 (No date or lab given) Summary: Salmonella typhimurium, TA1535, TA100, TA1537, TA98, TA1538; MITC, purity not given. 2.5 mg/plate was "toxic" and claimed to be non-mutagenic. Insufficient information for assessment. Incomplete, unacceptable. Gee, 7/25/85.

Mammalian systems

** 006 037169 "ZK 3,318 (Methyl Isothionate) Mutations Affecting the Hypoxanthine-Guanine Phosphoribosyl Transferase Locus in V79 Cells." (11/30/1984, Darmstadt Technical College for Nor-Am.) Chinese hamster V79/HGPRT; MITC, no purity given, Batch # 340/78; V79 exposed to 0, 0.1, 0.25, 0.5 or 1.0 without S-9; 0, 0.25, 0.5, 1.0 or 2.5 ug/ml with rat liver S-9 for 4 hours; no increase in mutation frequency in two trials; acceptable. Gee, 5/9/86.

Also see Methylenebis(thiocyanate) (SB no. 748).

SUMMARY: Data indicate that thiocyanates are negative for mutagenicity in bacteria but weakly positive in mouse lymphoma (two reports) but negative in Chinese hamster V79/HGPRT. The effect in mouse lymphoma may represent a "false positive" since no evidence for oncogenicity was reported in the rat and mouse studies, albeit those studies were conducted with methylisothiocyanate. Gee, 8/10/87.

MUTATIONS, CHROMOSOME

006 037168 "Testing of ZK 3.318 (Methylisothiocyanate) for Mutagenic Potential in the in vitro Chromosome Aberration Test." (1984, Lab. for Mutagenicity Testing - Germany, LMP 075B) Chromosome aberration, Chinese hamster V79 cells; MITC, no purity given; cells were exposed to 0, 0.25, 0.75 or 2.5 with Aroclor-induced rat liver S-9; 0, 0., 0.5 or 1.0 ug/ml without S-9 for 4 hours; harvested at 6, 12 and 28 hours after treatment - highest concentration only at 6 and 28 hours; weakly positive for increased aberrations (minus gaps) at 12 and 28 hours; unacceptable (no purity of test article, no concurrent cytotoxicity information, no definitions of aberrations as scored); possibly upgradeable.

Nonactivation		Control	0.1	0.5	1.0 ug/ml
% aberrations	- 12 hr	0.25	0.75	0.5	1.2
	- 28 hr	0	-	-	5.25

Activation		Control	0.25	0.75	2.5 ug/ml
% aberrations	- 12 hr	0.75	1.5	1.5	2.0
	- 28 hr	1.5	-	-	4.0

Aberrations were primarily breaks and some exchanges. JG, 5/9/86.

Also see Methylenebis(thiocyanate) (SB no. 748).

** 013 074317 "T102 Methyl Isothiocyanate: Sister Chromatid Exchange Assay in Chinese Hamster V79 Cells with Methyl Isothiocyanate Technical (MITC)," (Heidemann, A., Cytotest Cell Research GmbH & Co., KG, Project ID TB 88008, 10-12-88). Technical methylisothiocyanate (batch 370983, 95.6% pure) was assayed with Chinese hamster V79 cells for 4 hours, with and without S9 mix (from Aroclor 1254-induced male Wistar rat livers), at 0, 0.1, 2.0 and 3.5 µg/ml (no S9) or 0, 0.1, 2.5 and 5.0 µg/ml (with S9). The cells were then incubated an additional 24 hours with BrdU. Two experiments were conducted, each with duplicate cultures (25 metaphase cells/culture were scored). No increase in sister chromatid exchange was observed. **No adverse effects. Acceptable.** M. Silva, 7/22/91.

** 013 074318 "T103 Methyl Isothiocyanate: Chromosome Aberration Assay in Human Lymphocytes with Methyl Isothiocyanate Technical (MITC)," (Heidemann, A., Cytotest Cell Research GmbH & Co. KG, Project ID: TB 88007, 10-31-88). Phytohemagglutinin stimulated human peripheral blood lymphocytes were exposed, after 48 hours in culture, to methylisothiocyanate technical (95.6% pure) at 3.0 or 5.0 µg/ml for 4 hours. Cells were harvested at 24 and 48 hours after initiation of treatment (duplicate cultures; 100 metaphase cells per culture scored). There were no significant increases in chromosomal aberrations at any dose or time point. **No adverse effect. Acceptable.** M. Silva, 7/23/91.

SUMMARY: Two acceptable studies with MITC show no positive effect for chromosomal aberrations (human lymphocytes) or sister chromatid exchange (V79 cells). An earlier study for chromosomal aberrations, performed in V79 cells (1984), showed a weakly positive response. When performed with human lymphocytes, at even higher concentrations, the results were negative (1988). Therefore, MITC is considered not to induce cause adverse effects for chromosomal aberrations or sister chromatid exchanges. M. Silva, 7/29/91.

MUTATIONS, DNA

** 006 037170 "Evaluation of Methylisothiocyanate in the Rat Primary Hepatocyte Unscheduled DNA Synthesis Assay." (2/1985, Litton Bionetics, Project No. 20991.) Rat hepatocytes, UDS; MITC, technical grade, no purity given, lot # 340178; hepatocytes were exposed 18 hours to 0, 0.253, 0.505, 1.01, 2.53, 5.05, 10.1, 15.2 or 30.3 ug/ml with ^{3}H-TdR; no significant increase in net grains/nucleus is reported; complete and acceptable. Note: Purity of test article should be submitted. Gee, 5/12/86.

006 037173 "Microbial Mutagenicity Testing on Methyl Isothiocyanate." (1978, Inst. of Environ. Tox. - Japan.) Bacillus subtilis rec assay; MITC, 94.78%; minus activation only, single plate; at 0, 20, 100, 200, 500, 1000 or 2000 ug/disk in 20 ul; unacceptable, not upgradeable (no activation included, no justification for not using 5000 ug/disk, question of volatility of test article as discussed for Ames assay in same report - #037174, no inhibition of growth in either strain = no test.) Gee, 5/12/86.

50046-016 033907,-08 (No date or lab given) Summary: Bacillus subtilis, strain H17, M45; E. coli and S. typhimurium; MITC, no purity given; no info on doses, # of plates, etc. Incomplete, unacceptable (insufficient data). Gee, 7/25/85.

Also see Methylenebis(thiocyanate) (SB no. 748).

SUMMARY: No evidence with either compound for induction of unscheduled DNA synthesis in rat hepatocytes or transformation of Balb/3T3 cells (only tested without activation.) Gee, 8/10/87.

CONCLUSIONS: The long-term in vivo studies in animals were conducted with methylisothiocyanate (MITC). Only one possible adverse effect was reported in an in vitro genotoxicity study for aberrations with MITC. There were several positive effects with methylenebis(thiocyanate), both in vivo and in vitro. No long-term studies were conducted, however, with this thiocyanate. The collective evidence suggests that thiocyanates have a possible adverse effect on chromosomes both in vitro and in vivo. Gee, 8/10/87.

NEUROTOXICITY, HEN

No studies currently on file - not required at this time.

EPA ONE-LINERS

No EPA one-liners available as of August 5, 1987.